Effect of sugammadex and neostigmine on tracheal muscle: In vitro study

Sugammadex versus neostigmine in tracheal tissue

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Abstract

Aim: There are limited numbers of in vitro organ studies both neostigmine and, sugammadex. Up to date, we can reach no study in the literature comparing advantages and disadvantages of two agents in vitro. The study, we aimed to compare and demonstrate in vitro effects of neostigmine and sugammadex in rat trachea with basal and supramaximal tonus. Material and Method: A total of 24 adult male rats were divided into four groups: Group 1; Basal tonus+sugammadex, Group 2; Supramaximal contraction+sugammadex, Group 3; Basal tonus + neostigmine, Group 4; Supramaximal contraction+neostigmine. After anesthesia, trachea of each rats were removed and suspended in Krebs solution. After the vitality of the tissues was shown with acetylcholine and atropine, sugammadex was applied to group 1 and neostigmine to group 3 all in basal tonus. In other two groups, after supramaximal tonus with acetylcholine, sugammadex was applied to group 2, neostigmine to group 4. The contraction responses of each group were compared. Results: There was no significant change in comparison of the sugammadex groups ($p>0.05$). On the other hand, neostigmine increased tracheal tonus both in the basal tonus group (mean 25-40% ± 3.54), ($p <0.05$) and supramaximal tonus group (mean 15% ± 2.8) and were statistically significant ($p <0.05$). Discussion: In our study, neostigmine increased tracheal tone in both basal and supramaximal contractions. Neostigmine use, which may increase the risk of tracheal contractility, can be risky for surgical procedures. Therefore sugammadex may be preferred as there is no effect on tracheal tissue.

Keywords

Sugammadex; Neostigmine; Bronchospasm; Trachea; Isolated Tissue Bath; Rat

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Introduction

Anticholinesterases increase the amount of acetylcholine indirectly by inhibiting cholinesterase in the neuromuscular junction. As a result, acetylcholine and neuromuscular blockers compete each other in postsynaptic field and restore neuromuscular blockade [1].

Sugammadex is the first member, which has circular modified gamma cyclodextrin including 8 glucose molecules that returning effects of neuromuscular block agents [2]. Sugammadexformsa1:1 inclusion complex with NMBA (rocuronium >vecuronium>pancuronium), and encapsulates them and terminate their effects [3].

In addition to many side effects of neostigmine, the therapeutic index is rather small and the safety margin is low [4]. Among these side effects, bronchospasm is an undesired condition during anesthesia awakening [5]. This is an important complication, especially in high risk operations that trigger bronchospasm (such as bronchoscopy, tracheobronchial foreign body in children, tonsillectomy, and adenectomy).Sugammadex has been shown to have no effect on the bronchial smooth muscle [6].

In this study, we aimed to compare in vitro effects of neostigmine and sugammadex in rat trachea with normal and increased tonus and to base their findings on concrete data.

Material and Method

Animals

Four and six month old 24 male rats (350-400g) were obtained from Experimental Animal Center of Adnan Menderes University (ADU) and all experiments were performed in accordance with the principles and guidelines of ADU Animal Ethical Committee's approval (HADYEK 64583101/2017/065).

Experimental design

Krebs-Henseleit solution contains (g/L): glucose 2, MgSO4 0.41, KPO4 0.16, KCl 0.35, NaCl 6.9, CaCl 0.373, NaHC03 2.1 (ph: 7.4) in isolated tissue bath. The buffer solution was oxygenated with 95% O2 and 5% CO2 and 37°C temperature. During the equilibrium period in the organ bath, the Krebs solutions of the organs were washed 4 times in one hour (once a 15 minute period). During the equilibrium period, 1 g basal tension was slowly supplied.

All rats were anesthetized with 50mg/kg ketamine. While heart beat was continued after the anesthesia, trachea was removed with thoracotomy and sternotomy in 3mm-rings and suspended with 1g rest tension in 10 ml organ bath.

After the tracheas of rats were removed, all rats were decapitated and sacrificed. Isometric contractions of circular smooth muscles were measured with MAY FDT 10-A ® transducer. After the viability of the tissues was demonstrated with acetylcholine and atropine, the washed tissues were waited to reach the basal tonus.

There were 4 groups, including 6 tracheal tissues in each group.

Group 1: Sugammadex in tracheal tissue at basal tonus

Group 2: Sugammadex in tracheal tissue at supramaximal contraction

Group 3: Neostigmine in tracheal tissue at basal tonus

Group 4: Neostigmine in tracheal tissue at supramaximal contraction

The tissues were accepted vital if they released response to atropine after giving contraction response to acetylcholine [7]. Sugammadex ($9.2x10^{-4}$M) was applied to group 1 and neostigmine ($1.5x10^{-2}$M) to group 3 all in basal tonus. In the other two groups, after supramaximal tonus with acetylcholine, sugammadex was applied ($9.2x10^{-4}$M) to group 2, neostigmine ($1.5x10^{-2}$M) to group 4. Tissue tension was measured with the MAY GTA0303 GENIUS TRANSDUCER AMPLITUDE® and was recorded with the Acknowledge MP 100 ®.

Data presentation and statistics

The descriptive statistics and homogeneity tests were performed. According to the Shapiro-Wink analysis, logarithmic transformation was performed on the normal non-scattering data and the data were not normally dispersed. The Mann-Whitney U test was used for determining the differences between the groups. All the data were processed in SPSS and $p<0.05$ was accepted as statistically significant.

Results

There was no effect of sugammadex in neither basal nor supramaximal contractions (group 1: 0.213 ± 0.6, group 2: 0.373 ± 0.32) (Fig. 1) (p> 0.05). On the other hand, neostigmine increased the tonus mean by 8.216% ± 1.06 rate in group 3, while in the supramaximal contraction stimulated with Ach (group 4) the tonus increased by an additional rate of 8.005% ± 1.06 on supramaximal contraction (Fig. 1,2,3).

There was no statistical difference between group 1 and group 2 (sugammadex groups) (p> 0.05) (Figure 1). Similarly, there was no significance between group 3 and group 4 (neostigmine groups) (p> 0.05), (Figure 1). However, significance was found statistically in comparison of the sugammadex groups and the neostigmine groups (p=0.0002 between groups 1 and 3, p=0.0001 between groups 2 and 4), (Figure 1).

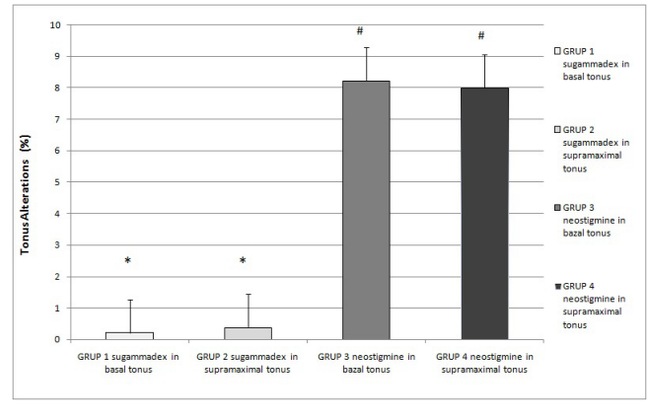

Figure 1. Percent alterations of tonus in all groups
* p>0,05, # p<0,05

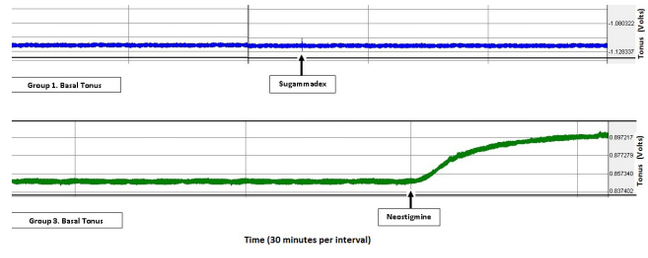

Figure 2. Graphics of tonus measurement in basal tonus groups.

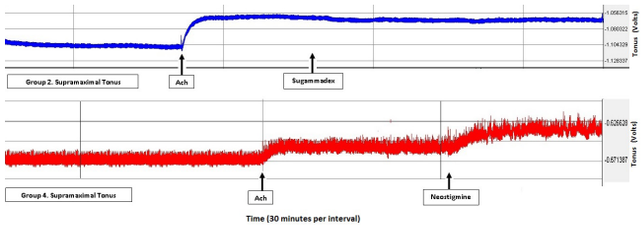

Figure 3. Graphics of tonus measurement in supramaximal tonus groups.

Discussion

In our study, we found that neostigmine increased the response to contraction in both the basal and supramaximal contraction, while sugammadex had no effect on tracheal muscle after neither basal nor supramaximal contractions.

Generally, responses of the tracheal and bronchial smooth muscle tissues are similar due to common histoembryonic structure in many in vitro studies [8-12], so we tried to discuss the issue on this context.

Neostigmine, as an anticholinesterase, has many side effects including bronchospasm, bradycardia, increase in secretions, accelerate peristalsis, residual block [5]. In addition, Eikermann et al. [13] have shown that neostigmine attenuates the activity of the upper respiratory tract dilator muscles. The constructive negative effect of neostigmine on bronchospasm has been emphasized in many other studies [13-15]. In our study, contraction effect on tracheal tissue of neostigmine, which can raise airway spasm clinically, could be shown in vitro.

Sugammadex is a new generation antagonist that removes the effect of the neuromuscular blocker by specifically encapsulating agent it. We found only one in vitro study that shows the effect of sugammadex on bronchi or tracheal muscle in literature [6]. In that study, Yoshiaka and al. mention that sugammadex has no muscle response on bronchial tissue after both the basal and increased tonus. We found compatible results showing no muscle response of sugammadex on tracheal tissue after basal or supramaximal tonus. Their and our similar results support that sugammadex gives similar muscle responses in trachea and bronchus.

In addition, laryngospasm ,bronchospasm and anaphylaxis related sugammadex were reported in a few clinical data [16-27]. Absence of tracheal tissue response in our study suggests that these clinical conditions related with other mechanisms except the tracheal tissue response.

Clinically there are many studies suggesting sugammadex instead of neostigmine in terms of risk of perioperative and postoperative bronchospasm, larigospasm and tracheal constriction [28-32]. Because no response on muscle, the data of our study were compatible with these clinical studies too.

Interestingly, bronchospasm warning for neostigmine is also present in its own prospectus. We based on tangible data that specific the response of tracheal tissue formed via the effect of neostigmine with the experimental study. Unfortunately, despite these side effects, anesthesiologists still have to use neostigmine because of the financial limits and developmental issues in new generation NMBA mentioned above. Anesthetists may be less dependent on anticholinesterases with increasing number of new generation NMBAs and the non-depolarizing muscle relaxants specific antagonists and perhaps they will be completely abandoned in the light of further studies.,

Moreover, this study can give inspire for hypotheses of further clinic trials advocating superiority of sugammadex, including risky surgical procedures and risky patients.

Neostigmine use, which may increase the risk of tracheal contractility, can be risky for surgical procedures. Therefore sugammadex may be preferred as there is no effect on tracheal tissue.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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